DAIDS
Bethesda, MD USA

POLICY

# Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements

Approval Date: 25 JUN 2009 No.: DWD-POL-CL-08.01
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## 1.0 PURPOSE

The purpose of this policy is to describe the special contents required in protocols of National Institute of Allergy and Infectious Disease (NIADS) Division of AIDS (DAIDS)-supported and/or -sponsored clinical research that include children. The requirement to submit these contents in sufficient detail to the approving Institutional Review Board (IRB)/ Ethics Committee (EC) will assist the IRB/EC in ensuring that the study is reviewed and conducted in accordance with applicable U.S. Federal laws and regulations.

## 2.0 SCOPE

This policy applies to all NIAID (DAIDS)-supported and/or -sponsored clinical research that intends to enroll children (including adolescents) in clinical research.

## 3.0 BACKGROUND

NIAID (DAIDS)-supported and/or -sponsored clinical research may involve children in the U.S. and, increasingly, children who reside in international settings. A significant portion of NIAID (DAIDS)-supported and/or -sponsored clinical research includes multi-center and network studies requiring centralized development of study (protocol) documents that are subsequently reviewed by multiple IRBs/ECs at diverse institutions. In order to ensure that NIAID (DAIDS)-supported and/or -sponsored clinical research is in compliance with all applicable laws and regulations governing the enrollment of children, DAIDS has established requirements for protocol content and requirements for clinical research sites to maintain written site policies and procedures. This policy describes the protocol document requirements. A companion policy, Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements, describes required written site policies and procedures and responsibilities of the Protocol Team, IRB/EC, Clinical Research Site (CRS) Leader, and the Principal Investigator (PI).

U.S. Regulatory Requirements

In addition to the regulatory requirements that list the Criteria for IRB Approval of Research[1], U.S. Federal regulations governing research in human subjects identify children as a vulnerable population and mandate additional scrutiny and protections prior to their involvement in research. These additional requirements found in 45 CFR 46, subpart D and 21 CFR 50, subpart D are described in this policy.

[1] 45 CFR §46.111 and 21 CFR §56.111

Categories

Three of the four categories of human research involving children may be approved by an IRB/EC. The four categories differ from one another according to the level of risk involved, the prospect of direct benefit to the research participants, and the anticipated research findings. For all four categories, the proposed research activity must satisfy the requirements for parental or guardian permission and child assent. Depending on the category, additional conditions must be met in order for the IRB/EC to approve the research activities (see Appendix 1 for additional information on risk/benefit categories).

## 4.0 DEFINITIONS

**Advocate:** An individual who has the background and experience to act in, and agrees to act in, the best interests of the child throughout the duration of the child's participation in the research and who is not associated in any way (except in the role as an advocate or member of the IRB/EC) with the research, the investigator(s), or the guardian organization. The advocate is in addition to any other individual acting on behalf of the child as guardian or in loco parentis. [2]

**Assent:** A child's affirmative agreement to participate in research. Mere failure to object should not, absent of affirmative agreement, be construed as assent.[3]

**Children:** Persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted.[4]

**Clinical Investigation:** Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA...or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. FDA has defined "clinical investigation" to be synonymous with "research". [5]

[2] 45 CFR §46.409(b) & 21 CFR §50.56(b)

[3] 45 CFR §46.402(b) and 21 CFR §50.3(n)

[4] 45 CFR §46.402(a) and 21 CFR §50.3(o)

[5] http://www.fda.gov/oc/gcP/comParison.html

**Clinical Research Site (CRS) Leader:** The onsite senior research scientist responsible for the administrative and scientific components of the CRS. The CRS leader is responsible for overall site activities, including day-to-day operations, performance, and compliance at the site level. (DAIDS)

**DAIDS supported:** Human subjects research activities would be considered to be supported by NIAID (DAIDS) under any one of the following circumstances:

(1) NIAID (DAIDS) provides direct funding to an institution via a grant, contract or cooperative agreement for the human subjects research activities; or (b) indirect funding via a subcontract executed under a NIAID (DAIDS) supported award to another institution; or

(2) NIAID (DAIDS) provides other tangible support for the human subject research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, management and distribution services; or

(3) NIAID (DAIDS) -supported central laboratory or data management center receives from other organization specimens or data for processing or analysis and the results or analyses will be used to direct involvement of some or all subjects in the conduct of the clinical research activities. (DAIDS)

**DAIDS sponsored:** NIAID (DAIDS) is responsible for the management (including submission of the Investigational New Drug Application (IND) to the Food and Drug Administration (FDA) and the initiation of the study) and oversight for the clinical trial or study. (DAIDS)

**Family Member:** Any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose association with the subject is the equivalent of a family relationship.[6]

[6] 21 CFR 50.3(m)

**Federalwide Assurance (FWA):** The Federalwide Assurance (FWA) is the only type of assurance of compliance accepted and approved by the Office for Human Research Protections (OHRP) for institutions engaged in non-exempt human subjects research conducted or supported by the U.S. Department of Health and Human Services (DHHS). Under an FWA, an institution commits to DHHS that it will comply with the requirements set forth in 45 CFR 46, as well as the Terms of Assurance.[7]

**Guardian:** An individual who is authorized to consent on behalf of a child to general medical care under applicable local law where the research is being conducted.[8]
For clinical trials conducted under FDA regulations, a guardian is an individual who is authorized to consent on behalf of a child to general medical care when general medical care includes participation in research under the applicable local law where the research is being conducted. A guardian is also an individual who is authorized to consent on behalf of a child to participate in research.[9]

**Minimal Risk:** The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.[10]

**Parent:** The child's biological or adoptive parent.[11]

**Permission**: The agreement of parent(s) or guardian to the participation of their child or ward in research.[12]

**Principal Investigator (PI):** The qualified person designated by the applicant institution to direct the research. PIs oversee the scientific and technical aspects of a grant and the day-to-day management of the research. (NIH)

[7] see http://www.hhs.gov.ohrp/humansubjects/assurance/filasurt.htm

[8] 45 CFR §46.402(e)

[9] 21 CFR §50.3(s)

[10] 45 CFR §46.102(i) and 21 CFR §50.3(k)

[11] 45 CFR §46.402(d) and 21 CFR §50.3(p)

[12] 45 CFR §46.402(c) and 21 CFR §50.3(r)

**Protocol:** A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.[13]

**Protocol Team:** A team of individuals comprised of grantees, investigators, statisticians, and other protocol support personnel who work to develop concepts into NIAID (DAIDS)-supported and/or -sponsored research studies. DAIDS medical officers may be involved as members of this team. (DAIDS)

**Ward:** A child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.[14]

For additional definitions see DAIDS Glossary:
http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Glossary

## 5.0 RESPONSIBILITIES

Protocol Team

The *Protocol Team* is responsible for providing sufficient detail in the protocol document to allow for the performance of a risk/benefit analysis and an assessment of the need for child assent.

IRB/EC

An *IRB/EC* identified on the Federalwide Assurance of the institution that is engaged in the research is responsible for the review of all clinical research enrolling children, and determining that all of the regulatory requirements are satisfied, including that risks to the child-participants are reasonable in relationship to anticipated benefits[15] and that there are adequate provisions for soliciting the assent of the child and permission of child-participants' parents or guardians[16]. The IRB/EC is responsible for determining when each child or all children are capable of

[13] ICH E6 1.44
[14] 21 CFR 50.3(q)
[15] 45 CFR §46.111 and Subpart D; 21 CFR 50, subpart D, 21 CFR §56.109; 21 CFR §56.111(2)
[16] 45 CFR §46.408 and 21 CFR §50.55

assent, whether and how assent must be documented, and when assent is not necessary or can be waived[17].

*CRS Leader*

The *CRS Leader* is responsible for ensuring that written policies and procedures are developed and maintained at the clinical research site that ensure that the enrollment of children into clinical research is consistent with applicable laws and regulations regarding initial and ongoing parental or guardian permission and child assent, that such procedures are in compliance with local institutional and IRB/EC policies and procedures, and that they are consistently applied.

Principle Investigator

The *Principal Investigator* is responsible for ensuring that DAIDS is informed of the IRB/EC determinations including risk/benefit analysis, IRB/EC approval of studies and amendments, and decisions regarding the need for child assent.

## 6.0 POLICY

6.1 In order to ensure that the requirements of 45 CFR 46, subpart D, Additional Protections for Children Involved as Subjects in Research and 21 CFR 50, subpart D, Additional Safeguards for Children in Clinical Investigations are satisfied, the Protocol Team will provide, in the protocol, the following information required for the IRB/EC to review and approve the protocol.

6.1.1 IRB/EC criteria that must be satisfied

6.1.1.1 A brief description of findings from previous related studies and justification in sufficient detail for the enrollment of children into the study.

6.1.1.2 A description of the research that would allow an IRB/EC assessment that the risks to participants are reasonable in relation to the anticipated benefits (if any) to participants, and the importance of the knowledge that may reasonably be expected to result;

6.1.1.3 Considerations for risk/benefit in sufficient details for the IRB/EC to determine into which of the four categories the

[17] 45 CFR §46.408 21 CFR §50.55

research activity falls (see Appendix 1 for details on risk/benefit categories and Appendix 2 for examples of risk category templated language)

6.1.1.3.1 Classifying a particular activity into one of these categories involves, among other things, determining whether the proposed research involves "minimal risk" to the participants. The Subpart D regulations rely on the definition of "minimal risk" provided in Subpart A of the regulations.

6.1.1.3.2 Determining that a research activity presents no more than minimal risk involves comparing the possible harms or discomforts experienced in normal daily life or during routine physical or psychological examinations or tests with the possible harms or discomforts that will be faced by participants as a consequence of research participation. The nature of the harms or discomforts (e.g., physical, psychological, legal) should be considered, as well as the chances that they will occur and the seriousness of their impact if they were to happen. Including measures to prevent or decrease the likelihood of harm or discomfort from the research may affect whether the proposed research activity involves no more than minimal risk. (See OHRP FAQs on Research with Children.*)*

6.1.2 When the child reaches legal age of consent

Recommendations, where appropriate, for continuation of research participation when the child reaches legal age of consent.

If a study involves children who may reach the legal age of consent during their participation in the research, the Protocol Team will identify whether there is a need to obtain the legally effective informed consent for the now-adult subject. This may be appropriate, for example, when the research involves ongoing interactions or interventions with the participants after they have

reached the legal age of consent. When a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the participant's involvement in the research is no longer regulated by the requirements of Subpart D regarding parental or guardian permission and subject assent. (See OHRP FAQs on Research with Children and DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.)

6.1.3 Obtaining informed consent from other individuals involved in research

Recommendations for obtaining informed consent from other individuals in addition to enrolled children, such as parents or family members who are human subjects in the research.

When family members of children enrolled in the research are asked to provide identifiable private information about themselves for research purposes, these individuals are considered human subjects in the research and they must also give their informed consent unless the IRB/EC finds and documents the criteria for waiver of informed consent to be met.

6.1.4 Information when enrolling wards

Additional information to be provided to the IRB/EC for enrolling children in the research who are wards of the State or any other agency, institution, or entity under the following conditions:

6.1.4.1 when there are definite plans to enroll such participants for research; and

6.1.4.2 when the research will be approved by the IRB/EC under categories 45 CFR §46.406, 21 CFR §50.53, 45 CFR §46.407, and/or 21 CFR §50.54.

The information provided to the IRB/EC should include if the research is:

1. Related to the participants status as wards; or

2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(See Appendix 3 and DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.)

6.1.5 Recommendations for obtaining parental or guardian permission

As appropriate, recommendations for obtaining parental or guardian permission based upon the regulations at 45 CFR §46.408 and 21 CFR §50.55 for review and approval by the IRB/EC.

(See Appendix 1 for details on parental permission requirements associated with each risk/benefit category, Appendix 2 for examples of templated language associated with parental/guardian permission choices, and DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.)

6.1.6 Waiver of parental/guardian permission

If a waiver of parental/guardian permission is likely to be requested by the site investigators in accordance with the provisions at 45 CFR §46.116(c) or §46.116(d), sufficient detail to justify the waiver.

In accordance with the regulations, the IRB/EC must find and document that the criteria for the waiver are met.

NOTE: The provisions for waiver of parental/guardian permission in U.S. Food and Drug Administration (FDA) regulated clinical investigations are limited to 21 CFR §50.23, Exception from General Requirements and 21 CFR §50.24, Exception from Informed Consent Requirements for Emergency Research.

When the research is not FDA-regulated and does not meet the requirement for the waiver under 45 CFR §46.116(c) or §46.116(d), the IRB/EC may waive the requirements for obtaining parental/guardian permission if it determines that the research protocol is designed for a condition or for a subject population for

which parental/guardian permission is not a reasonable requirement, to protect participants provided an appropriate mechanism for protecting the children who will participate in the research is substituted. In addition, the waiver must be consistent with Federal, State or local law (see 45 CFR §46.408(c)).

The conditions under which parental permission may be waived and examples of substitute protection mechanisms can be found in Appendix 4. An example of when waiver of parental/guardian permission may be appropriate would be the conduct of a non-FDA regulated study of abused children.

6.1.7 Waiver of documentation of parental/guardian permission

If it is likely that the site investigator will request waiver of documentation of parental/guardian permission, sufficient details for the IRB/EC to make the findings for approval of the waiver.

In accordance with 45 CFR §46.117(c)(2) and 21 CFR §56.109(c*)* the IRB/EC may waive the requirements for documentation of parental/guardian permission for research that presents no more than minimal risk of harm to participants and involves no procedure for which written consent is normally required outside of the research context. However, the IRB/EC may require the site investigator to provide parents/guardians with a written statement regarding the research.

In addition, for non-FDA regulated clinical investigations, if the only record linking the child and the research would be the assent document and the principal risk would be potential harm resulting from a breach in confidentiality, then the documentation of parental/guardian permission can be waived. Each parent/guardian will be asked whether they want documentation linking the child with the research and the parent/guardian's wishes will govern. However, the IRB/EC may require the site investigator to provide parents/guardians with a written statement regarding the research. See 45 CFR §46.117(c)(1) for further information on this type of waiver of documentation of parental/guardian permission.

NOTE: Studies that are subject to FDA regulation are not eligible for a waiver of documentation of parental/guardian permission unless they meet the criteria at 21 CFR §50.27 or 21 CFR §56.109(c).

6.1.8 Child Assent

Recommendations whether eligible children could be capable of providing assent and if so, indicate that the IRB/EC-approved process for obtaining and documenting the child's assent will be followed. (see DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements.)

The provisions to obtain child assent may be made for all children involved in the research or to address each child as deemed appropriate by the IRB/EC. A study that may enroll children over a wide age range is an example of a study that may have different assent requirements.

6.1.8.1 For eligible children who are adolescents, the assent requirements would more closely resemble that of an adult consent process.

6.1.8.2 Where children are less mature or of an age that limits their ability to understand, the process would involve more description of what the actual experience of participation in research is likely to be, how long it will take, or whether it might involve any pain or discomfort.

6.1.9 Waiver of Child Assent

If it is likely that a waiver of assent will be requested from the IRB/EC, sufficient details in the protocol for the IRB/EC to make the finding for approval of the waiver.

Assent may be waived by the IRB/EC if one of the three following circumstances is met:

1) the capability of some or all of the children is so limited that they cannot reasonably be consulted;

2) the intervention or procedure involved holds out the prospect of direct benefit to the health or well-being of the child and is only available in the research (they may document this determination and submit it to the IRB/EC for approval);

3) the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR §46.116(c) or 45 CFR §46.116(d).

(See Appendix 2 for examples of templated language associated with child assent choices and Appendix 4 for regulations pertaining to waiving child assent.)

6.2. Research that is otherwise exempt from IRB/EC review

The Protocol Team must take into account that some research activities that would be exempt if the research participants were adults requires IRB/EC review if the research activities involve children (45 CFR §46.101(b) and 21 CFR §56.104).

Examples of research **not** exempt from IRB/EC review when conducted in children include:

1. surveys;
2. interviews; and
3. research involving public observation when the investigator(s) participates in the activities being observed.

## 7.0 REFERENCES

Code of Federal Regulations, Title 45, Part 46 Protection of Human Subjects
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Code of Federal Regulations, Title 45 CFR Part 46, subpart D, Additional Protections for Children Involved as Subjects in Research
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Code of Federal Regulations, Title 21 CFR Part 50 Protection of Human Subjects
http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr50_06.html

Code of Federal Regulations, Title 21 CFR Part 50, subpart D, Additional Safeguards for Children in Clinical Investigations
http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr50_06.html

21 CFR 56, Institutional Review Boards
http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr56_06.html

Office for Human Research Protections (OHRP) FAQs on Research with Children
http://www.hhs.gov/ohrp/policy/index.html#children

Federal Register: April 24, 2001 (Volume 66, Number 79) Additional Safeguards for Children in Clinical Investigations of FDA-regulated Products
http://www.fda.gov/OHRMS/DOCKETS/98fr/042401a.pdf

DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements

## 8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group at: NIAIDOPCROPOLICYGROUP@mail.nih.gov

## 9.0 AVAILABILITY

This policy is available electronically at the following URL:
http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm

## 10.0 CHANGE SUMMARY

This policy is the first version. It does not supersede any other version.

## 11.0 APPENDICIES

Appendix 1 Risk/Benefit Categories [CL.201]
Appendix 2 Examples of Templated Language [CL.202]
Appendix 3 Wards[ CL.203]
Appendix 4 Waivers of Parental/Guardian Permission or Child Assent [CL.204]

## 12.0 APPROVAL

/Richard Hafner, MD/
Richard Hafner